

ARIXTRA®
(fondaparinux sodium) Injection

SPINAL/EPIDURAL HEMATOMAS

When neuraxial anesthesia (epidural/spinal anesthesia) or spinal puncture is employed, patients anticoagulated or scheduled to be anticoagulated with low molecular weight heparins, heparinoids or fondaparinux sodium for prevention of thromboembolic complications are at risk of developing an epidural or spinal hematoma which can result in long-term or permanent paralysis.

The risk of these events is increased by the use of indwelling epidural catheters for administration of analgesia or by the concomitant use of drugs affecting hemostasis such as non-steroidal anti-inflammatory drugs (NSAIDs), platelet inhibitors, or other anticoagulants. The risk also appears to be increased by traumatic or repeated epidural or spinal puncture.

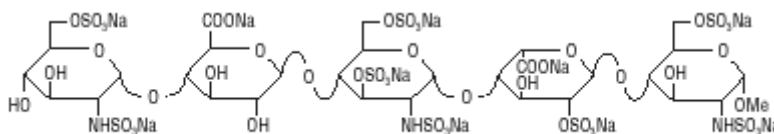
Patients should be frequently monitored for signs and symptoms of neurological impairment. If neurologic compromise is noted, urgent treatment is necessary.

The physician should consider the potential benefit versus risk before neuraxial intervention in patients anticoagulated or to be anti-coagulated for thromboprophylaxis (see also **WARNINGS: Hemorrhage** and **PRECAUTIONS: Drug Interactions**).

DESCRIPTION

ARIXTRA® (fondaparinux sodium) Injection is a sterile solution containing fondaparinux sodium. It is a synthetic and specific inhibitor of activated Factor X (Xa). Fondaparinux sodium is methyl O-2-deoxy-6-O-sulfo-2-(sulfoamino)- α -D-glucopyranosyl-(1 \rightarrow 4)-O- β -D-glucopyranuronosyl-(1 \rightarrow 4)-O-2-deoxy-3,6-di-O-sulfo-2-(sulfoamino)- α -D-glucopyranosyl-(1 \rightarrow 4)-O-2-O-sulfo- α -L-idopyranuronosyl-(1 \rightarrow 4)-2-deoxy-6-O-sulfo-2-(sulfoamino)- α -D-glucopyranoside, decasodium salt.

The molecular formula of fondaparinux sodium is $C_{31}H_{43}N_3Na_{10}O_{49}S_8$ and its molecular weight is 1728. The structural formula is provided below:



ARIXTRA is supplied as a sterile, preservative-free injectable solution for subcutaneous use.

Each single dose, prefilled syringe of ARIXTRA, affixed with an automatic needle protection system, contains 2.5 mg of fondaparinux sodium in 0.5 mL of an isotonic solution of sodium chloride and water for injection. The final drug product is a clear and colorless liquid with a pH between 5.0 and 8.0.

CLINICAL PHARMACOLOGY

Pharmacodynamics

Mechanism of Action: The antithrombotic activity of fondaparinux sodium is the result of antithrombin III (ATIII)-mediated selective inhibition of Factor Xa. By selectively binding to ATIII, fondaparinux sodium potentiates (about 300 times) the innate neutralization of Factor Xa by ATIII. Neutralization of Factor Xa interrupts the blood coagulation cascade and thus inhibits thrombin formation and thrombus development.

Fondaparinux sodium does not inactivate thrombin (activated Factor II) and has no known effect on platelet function. At the recommended dose, fondaparinux sodium does not affect fibrinolytic activity or bleeding time.

Anti-Xa Activity: The pharmacodynamics/pharmacokinetics of fondaparinux sodium are derived from fondaparinux plasma concentrations quantified via anti-Factor Xa activity. Only fondaparinux can be used to calibrate the anti-Xa assay. (The international standards of heparin or LMWH are not appropriate for this use.) As a result, the activity of fondaparinux sodium is expressed as milligrams (mg) of the fondaparinux calibrator. The anti-Xa activity of the drug increases with increasing drug concentration, reaching maximum values in approximately 3 hours.

Pharmacokinetics

Absorption: Fondaparinux sodium administered by subcutaneous injection is rapidly and completely absorbed (absolute bioavailability is 100%). Following a single subcutaneous dose of fondaparinux sodium 2.5 mg in young male subjects, C_{max} of 0.34 mg/L is reached in approximately 2 hours. In patients undergoing treatment with fondaparinux sodium injection 2.5 mg, once daily, the peak steady-state plasma concentration is, on average, 0.39–0.50 mg/L and is reached approximately 3 hours post-dose. In these patients, the minimum steady-state plasma concentration is 0.14–0.19 mg/L.

Distribution: In healthy adults, intravenously or subcutaneously administered fondaparinux sodium distributes mainly in blood and only to a minor extent in extravascular fluid as evidenced by steady state and non-steady state apparent volume of distribution of 7–11 L. Similar fondaparinux distribution occurs in patients undergoing elective hip surgery or hip fracture surgery. *In vitro*, fondaparinux sodium is highly (at least 94%) and specifically bound to antithrombin III (ATIII) and does not bind significantly to other plasma proteins (including platelet Factor 4 [PF4]) or red blood cells.

Metabolism: *In vivo* metabolism of fondaparinux has not been investigated since the majority of the administered dose is eliminated unchanged in urine in individuals with normal kidney function.

Elimination: In individuals with normal kidney function fondaparinux is eliminated in urine mainly as unchanged drug. In healthy individuals up to 75 years of age, up to 77% of a single subcutaneous or intravenous fondaparinux dose is eliminated in urine as unchanged drug in 72 hours. The elimination half-life is 17–21 hours.

Special Populations

Renal Impairment: Fondaparinux elimination is prolonged in patients with renal impairment since the major route of elimination is urinary excretion of unchanged drug. In patients undergoing elective hip surgery or hip fracture surgery, the total clearance of fondaparinux is approximately 25% lower in patients with mild renal impairment (creatinine clearance 50 to 80 mL/min), approximately 40% lower in patients with moderate renal impairment (creatinine clearance 30 to 50 mL/min) and approximately 55% lower in patients with severe renal impairment (<30 mL/min) compared to patients with normal renal function (see **CONTRAINDICATIONS and WARNINGS: Renal Impairment**).

Hepatic Impairment: The pharmacokinetic properties of fondaparinux have not been studied in patients with hepatic impairment.

Elderly Patients: Fondaparinux elimination is prolonged in patients over 75 years old. In studies evaluating fondaparinux sodium 2.5 mg in hip fracture surgery or elective hip surgery, the total clearance of fondaparinux was approximately 25% lower in patients over 75 years old as compared to patients less than 65 years old.

Patients Weighing Less Than 50 kg: Total clearance of fondaparinux sodium is decreased by approximately 30% in patients weighing less than 50 kg (see **CONTRAINDICATIONS**).

Gender: The pharmacokinetic properties of fondaparinux sodium are not significantly affected by gender.

Race: Pharmacokinetic differences due to race have not been studied prospectively. However, studies performed in Asian (Japanese) healthy subjects did not reveal a different pharmacokinetic profile compared to Caucasian healthy subjects. Similarly, no plasma clearance differences were observed between Black and Caucasian patients undergoing orthopedic surgery.

Drug Interactions: see **PRECAUTIONS: Drug Interactions**.

CLINICAL STUDIES

Prophylaxis of Thromboembolic Events Following Hip Fracture Surgery

In a randomized, double-blind, clinical trial in patients undergoing hip fracture surgery, ARIXTRA (fondaparinux sodium) Injection 2.5 mg SC once daily was compared to enoxaparin sodium 40 mg SC once daily which is not approved for use in patients undergoing hip fracture surgery. A total of 1711 patients were randomized and 1673 were treated. Patients ranged in age from 17–101 years (mean age 77 years) with 25% men and 75% women. Patients were 99% Caucasian, 1% other races. Patients with multiple traumas affecting more than one organ system, serum creatinine level more than 2 mg/dL (180 µmol/L), or platelet count less than 100,000/mm³ were excluded from the trial. ARIXTRA was initiated after surgery in 88% of patients (mean 6 hrs.) and enoxaparin sodium was initiated after surgery in 74% of patients (mean 18 hrs.). For both drugs, treatment was continued for 7 ± 2 days. The primary efficacy endpoint, venous thromboembolism (VTE), was a composite of documented deep vein thrombosis (DVT) and/or documented symptomatic pulmonary embolism (PE) reported up to Day 11. The efficacy data are provided in Table 1 below and demonstrate that under the conditions of the trial fondaparinux sodium was associated with a VTE rate of 8.3% compared with a VTE rate of 19.1% for enoxaparin sodium for a relative risk reduction of 56% (95% CI: 39%, 70%; p < 0.001).

Major bleeding episodes occurred in 2.2% of ARIXTRA patients and 2.3% of enoxaparin sodium patients (see Tables 5 and 6 under **ADVERSE REACTIONS: Hemorrhage**).

Table 1: Efficacy of ARIXTRA Injection In the Peri-operative Prophylaxis of Thromboembolic Events Following Hip Fracture Surgery

	Peri-operative Prophylaxis (Day 1 to Day 7±2 post-surgery)	
Endpoint	Fondaparinux Sodium 2.5 mg SC once daily¹	Enoxaparin Sodium 40 mg SC once daily^{1,2}
All Treated Hip Fracture Surgery Patients	N = 831	N = 840
All Evaluable³ Hip Fracture Surgery Patients		
VTE ⁴	52/626 8.3% ⁵ (6.3, 10.8) ⁶	119/624 19.1% (16.1, 22.4)
All DVT	49/624 7.9% ⁵ (5.9, 10.2)	117/623 18.8% (15.8, 22.1)
Proximal DVT	6/650 0.9% ⁵ (0.3, 2.0)	28/646 4.3% (2.9, 6.2)
Symptomatic PE	3/831 0.4% ⁷ (0.1, 1.1)	3/840 0.4% (0.1, 1.0)
1. ARIXTRA was initiated after surgery in 88% of patients (mean 6 hrs.) and enoxaparin sodium was initiated after surgery in 74% of patients (mean 18 hrs.). 2. Not approved for use in patients undergoing hip fracture surgery. 3. Evaluable patients were those who were treated and underwent the appropriate surgery (ie. hip fracture surgery of the upper third of the femur), with an adequate efficacy assessment up to Day 11. 4. VTE was a composite of documented DVT and/or documented symptomatic PE reported up to Day 11. 5 p value < 0.001 6 Numbers in parentheses indicate 95% confidence interval 7 p value: NS		

Extended Prophylaxis of Thromboembolic Events Following Hip Fracture Surgery

In a noncomparative, unblinded manner, 737 patients undergoing hip fracture surgery were initially treated during the peri-operative period with ARIXTRA 2.5 mg once daily for 7 ± 1 days. Eighty one (81) of the 737 patients were not eligible for randomization into the 3-week double-blind period. Three hundred twenty six (326) patients and 330 patients were randomized to receive ARIXTRA 2.5 mg once daily or placebo, respectively in or out of the hospital for 21 ± 2 days. Patients ranged in age from 23 to 96 years (mean age 75 years) and were 29% men and 71% women. Patients were 99% Caucasian and 1% other races. Patients with multiple traumas affecting more than one organ system or serum creatinine level more than 2 mg/dL (180 μ mol/L) were excluded from the trial. The primary efficacy endpoint, venous thromboembolism (VTE), was a composite of documented deep vein thrombosis (DVT) and/or documented symptomatic pulmonary embolism (PE) reported for up to 24 days following randomization. The efficacy data are provided in Table 2 below and demonstrate that extended prophylaxis with fondaparinux sodium was associated with a VTE rate of 1.4% compared with a VTE rate of 35.0% for placebo for a relative risk reduction of 95.9% (95% CI=[-99.7; -87.2], $p < 0.0001$). Major bleeding rates during the 3-week extended prophylaxis period for ARIXTRA (2.4%) and placebo (0.6%) are provided in Tables 5 and 6 (see **ADVERSE REACTIONS: Hemorrhage**).

Table 2: Efficacy of ARIXTRA Injection In the Extended Prophylaxis of Thromboembolic Events Following Hip Fracture Surgery

Endpoint	Extended Prophylaxis (Day 8 to Day 28±2 post-surgery)	
	Fondaparinux Sodium 2.5 mg SC once daily	Placebo SC once daily
All Randomized Treated Hip Fracture Surgery Patients	N = 326	N = 330
All Randomized Evaluable Hip Fracture Surgery Patients¹		
VTE ²	3/208 1.4% ³ (0.3, 4.2) ⁴	77/220 35.0% (28.7, 41.7)
All DVT	3/208 1.4% ³ (0.3, 4.2)	74/218 33.9% (27.7, 40.6)
Proximal DVT	2/221 0.9% ³ (0.1, 3.2)	35/222 15.8% (11.2, 21.2)
Symptomatic VTE (all)	1/326 0.3% ⁵ (0.0, 1.7)	9/330 2.7% (1.3, 5.1)
Symptomatic PE	0/326 0.0% ⁶ (0.0, 1.1)	3/330 0.9% (0.2, 2.6)
¹ Evaluable patients were those who were treated in the post-randomization period, with an adequate efficacy assessment for up to 24 days following randomization. ² VTE was a composite of documented DVT and/or documented symptomatic PE reported for up to 24 days following randomization ³ p value < 0.001 ⁴ Number in parentheses indicates 95% confidence interval. ⁵ p value = 0.021 ⁶ p value = NS		

Prophylaxis of Thromboembolic Events Following Hip Replacement Surgery

In two randomized, double-blind, clinical trials in patients undergoing hip replacement surgery, ARIXTRA 2.5 mg SC once daily was compared to either enoxaparin sodium 30 mg SC every 12 hours (Study 1) or to enoxaparin sodium 40 mg SC once a day (Study 2). In Study 1, a total of 2275 patients were randomized and 2257 were treated. Patients ranged in age from 18 to 92 years (mean age 65 years) with 48% men and 52% women. Patients were 94% Caucasian, 4% Black, <1% Asian, and 2% others. In Study 2, a total of 2309 patients were randomized and 2273 were treated. Patients ranged in age from 24 to 97 years (mean age 65 years) with 42% men and 58% women. Patients were 99% Caucasian, and 1% other races. Patients with serum creatinine level more than 2 mg/dL (180 μ mol/L), or platelet count less than 100,000/mm³ were excluded from both trials. In Study 1, ARIXTRA was initiated 6 ± 2 hours (mean 6.5 hrs) after surgery in 92% of patients and enoxaparin sodium was initiated 12 to 24 hours (mean 20.25 hrs) after surgery in 97% of patients. In Study 2, ARIXTRA was initiated 6 ± 2 hours (mean 6.25 hrs) after surgery in 86% of patients and enoxaparin sodium was initiated 12 hours before surgery in 78% of patients. The first post-operative enoxaparin sodium dose was given before 12 hours after surgery in 60% of patients and 12 to 24 hours after surgery in 35% of patients with a mean of 13 hrs. For both studies, both study treatments were continued for 7 ± 2 days. The efficacy data are provided in Table 3 below. Under the conditions of Study 1, fondaparinux sodium was associated with a VTE rate of 6.1% compared with a VTE rate of 8.3% for enoxaparin sodium for a relative risk reduction of 26% (95% CI: -11%, 53%; $p = \text{NS}$). Under the conditions of Study 2, fondaparinux sodium was associated with a VTE rate of 4.1% compared with a VTE rate of 9.2% for enoxaparin sodium for a relative risk reduction of 56% (95% CI: 33%, 73%; $p < 0.001$). For the two studies combined, the major bleeding episodes occurred in 3.0% of ARIXTRA patients and 2.1% of enoxaparin sodium patients (See Tables 5 and 6 under **ADVERSE REACTIONS: Hemorrhage**).

Table 3: Efficacy of ARIXTRA Injection In the Prophylaxis of Thromboembolic Events Following Hip Replacement Surgery

	Study 1		Study 2	
Endpoint	Fondaparinux Sodium 2.5 mg SC once daily¹	Enoxaparin Sodium 30 mg SC every 12 hr³	Fondaparinux Sodium 2.5 mg SC once daily²	Enoxaparin Sodium 40 mg SC once daily⁴
All Treated Hip Replacement Surgery Patients	N = 1126	N = 1128	N = 1129	N = 1123
All Evaluable⁵ Hip Replacement Surgery Patients				
VTE ⁶	48/787 6.1% ⁷ (4.5, 8.0) ⁸	66/797 8.3% (6.5, 10.4)	37/908 4.1% ¹⁰ (2.9, 5.6)	85/919 9.2% (7.5, 11.3)
All DVT	44/784 5.6% ⁹ (4.1, 7.5)	65/796 8.2% (6.4, 10.3)	36/908 4.0% ¹⁰ (2.8, 5.4)	83/918 9.0% (7.3, 11.1)
Proximal DVT	14/816 1.7% ⁷ (0.9, 2.9)	10/830 1.2% (0.6, 2.2)	6/922 0.7% ¹¹ (0.2, 1.4)	23/927 2.5% (1.6, 3.7)
Symptomatic PE	5/1126 0.4% ⁷ (0.1, 1.0)	1/1128 0.1% (0.0, 0.5)	2/1129 0.2% ⁷ (0.0, 0.6)	2/1123 0.2% (0.0, 0.6)
1. In Study 1, ARIXTRA was initiated after surgery in 92% of patients (mean 6.5 hrs) 2. In Study 2, ARIXTRA was initiated after surgery in 86% of patients (mean 6.25 hrs) 3. In Study 1, enoxaparin sodium was initiated after surgery in 97% of patients (mean 20.25 hrs) 4. In Study 2, enoxaparin sodium was initiated before surgery in 78% of patients. The first postoperative dose was given a mean of 13 hrs after surgery) 5. Evaluable patients were those who were treated and underwent the appropriate surgery (ie. hip replacement surgery), with an adequate efficacy assessment up to Day 11. 6. VTE was a composite of documented DVT and/or documented symptomatic PE reported up to Day 11. 7. p value versus enoxaparin sodium: NS 8. Number in parentheses indicates 95% confidence interval 9. p value versus enoxaparin sodium in study 1: <0.05 10. p value versus enoxaparin sodium in study 2: <0.001 11. p value versus enoxaparin sodium in study 2: <0.01				

Prophylaxis of Thromboembolic Events Following Knee Replacement Surgery

In a randomized, double-blind, clinical trial in patients undergoing knee replacement surgery (i.e., surgery requiring resection of the distal end of the femur or proximal end of the tibia), ARIXTRA 2.5 mg SC once daily was compared to enoxaparin sodium 30 mg SC every 12 hours. A total of 1049 patients were randomized and 1034 were treated. Patients ranged in age from 19 to 94 years (mean age 68 years) with 41% men and 59% women. Patients were 88% Caucasian, 8% Black, <1% Asian, and 3% others. Patients with serum creatinine level more than 2 mg/dL (180 µmol/L), or platelet count less than 100,000/mm³ were excluded from the trial. ARIXTRA was initiated 6 ± 2 hours (mean 6.25 hrs) after surgery in 94% of patients and enoxaparin sodium was initiated 12 to 24 hours (mean 21 hrs) after surgery in 96% of patients. For both drugs, treatment was continued for 7 ± 2 days. The efficacy data are provided in Table 4 below and demonstrate that under the conditions of the trial, fondaparinux sodium was associated with a VTE rate of 12.5% compared with a VTE rate of 27.8% for enoxaparin sodium for a relative risk reduction of 55% (95% CI: 36%, 70%; p <0.001). Major bleeding episodes

occurred in 2.1% of ARIXTRA patients and 0.2% of enoxaparin sodium patients (see Tables 5 and 6 under **ADVERSE REACTIONS: Hemorrhage**).

Table 4: Efficacy of ARIXTRA Injection In the Prophylaxis of Thromboembolic Events Following Knee Replacement Surgery

Endpoint	Fondaparinux Sodium 2.5 mg SC once daily ¹	Enoxaparin Sodium 30 mg SC every 12 hrs ²
All Treated Knee Replacement Surgery Patients	N = 517	N = 517
All Evaluable³ Knee Replacement Surgery Patients		
VTE ⁴	45/361 12.5% ⁵ (9.2, 16.3) ⁶	101/363 27.8% (23.3, 32.7)
All DVT	45/361 12.5% ⁵ (9.2, 16.3)	98/361 27.1% (22.6, 32.0)
Proximal DVT	9/368 2.4% ⁷ (1.1, 4.6)	20/372 5.4% (3.3, 8.2)
Symptomatic PE	1/517 0.2% ⁷ (0.0, 1.1)	4/517 0.8% (0.2, 2.0)
1. Patients randomized to ARIXTRA 2.5 mg received the first injection 6 ± 2 hours after surgery providing that hemostasis had been achieved. 2. Patients randomized to enoxaparin sodium received the first injection at 21 ± 2 hours after surgery closure providing that hemostasis had been achieved. 3. Evaluable patients were those who were treated and underwent the appropriate surgery (ie. knee replacement surgery), with an adequate efficacy assessment up to Day 11. 4. VTE was a composite of documented DVT and/or documented symptomatic PE reported up to Day 11. 5 p value < 0.001 6 Number in parenthesis indicates 95% confidence interval 7 p value: NS		

INDICATIONS AND USAGE

ARIXTRA (fondaparinux sodium) Injection is indicated for the prophylaxis of deep vein thrombosis, which may lead to pulmonary embolism:

- in patients undergoing hip fracture surgery, including extended prophylaxis;
- in patients undergoing hip replacement surgery;
- in patients undergoing knee replacement surgery.

CONTRAINDICATIONS

ARIXTRA (fondaparinux sodium) Injection is contraindicated in patients with severe renal impairment (creatinine clearance <30mL/min). ARIXTRA is eliminated primarily by the kidneys, and such patients are at increased risk for major bleeding episodes (see WARNINGS: Renal Impairment).

ARIXTRA is contraindicated in patients with body weight <50 kg. During randomized clinical trials of the peri-operative period occurrence of major bleeding was doubled in patients with body weight <50 kg compared with those with body weight ≥50 kg (5.4% vs. 2.1%).

The use of ARIXTRA is contraindicated in patients with active major bleeding, bacterial endocarditis, in patients with thrombocytopenia associated with a positive *in vitro* test for anti-platelet antibody in the presence of fondaparinux sodium, or in patients with known hypersensitivity to fondaparinux sodium.

WARNINGS

ARIXTRA (fondaparinux sodium) Injection is not intended for intramuscular administration.

ARIXTRA cannot be used interchangeably (unit for unit) with heparin, low molecular weight heparins or heparinoids, as they differ in manufacturing process, anti-Xa and anti-IIa activity, units, and dosage. Each of these medicines has its own instructions for use.

Renal Impairment

The risk of hemorrhage increases with increasing renal impairment. Occurrences of major bleeding in patients with normal renal function, mild renal impairment, moderate renal impairment, and severe renal impairment have been found to be 1.6% (25/1565), 2.4% (31/1288), 3.8% (19/504), and 4.8% (4/83), respectively (see **CLINICAL PHARMACOLOGY: Special Populations, Renal Impairment and CONTRAINDICATIONS**).

Therefore, ARIXTRA is contraindicated in patients with severe renal impairment (creatinine clearance <30 mL/min) and should be used with caution in patients with moderate (creatinine clearance 30-50 mL/min).

Renal function should be assessed periodically in patients receiving the drug. ARIXTRA should be discontinued immediately in patients who develop severe renal impairment or labile renal function while on therapy. After discontinuation of ARIXTRA, its anticoagulant effects may persist for 2–4 days in patients with normal renal function (i.e., at least 3–5 half-lives). The anticoagulant effects of ARIXTRA may persist even longer in patients with renal impairment (see **CLINICAL PHARMACOLOGY**).

Hemorrhage

ARIXTRA Injection, like other anticoagulants, should be used with extreme caution in conditions with increased risk of hemorrhage, such as congenital or acquired bleeding disorders, active ulcerative and angiodysplastic gastrointestinal disease, hemorrhagic stroke, or shortly after brain, spinal, or ophthalmological surgery, or in patients treated concomitantly with platelet inhibitors.

Laboratory Testing

Because routine coagulation tests such as Prothrombin Time (PT) and Activated Partial Thromboplastin Time (aPTT) are relatively insensitive measures of ARIXTRA activity and international standards of heparin or LMWH are not calibrators to measure anti-Factor Xa activity of ARIXTRA, if during ARIXTRA therapy unexpected changes in coagulation parameters or major bleeding occurs, ARIXTRA should be discontinued (see **PRECAUTIONS: Laboratory Tests**).

Neuraxial Anesthesia and Post-operative Indwelling Epidural Catheter Use

Spinal or epidural hematomas, which may result in long-term or permanent paralysis, can occur with the use of anticoagulants and neuraxial (spinal/epidural) anesthesia or spinal puncture. The risk of these events may be higher with post-operative use of indwelling epidural catheters or concomitant use of other drugs affecting hemostasis such as NSAIDs (see **Boxed Warning for Spinal/Epidural Hematomas**).

Thrombocytopenia: Thrombocytopenia can occur with the administration of ARIXTRA. Moderate thrombocytopenia (platelet counts between 100,000/mm³ and 50,000/mm³) occurred at a rate of 2.9% in patients given ARIXTRA 2.5 mg in clinical trials. Severe thrombocytopenia (platelet counts less than 50,000/mm³) occurred at a rate of 0.2% in patients given ARIXTRA 2.5 mg in clinical trials. During extended prophylaxis, no cases of moderate or severe thrombocytopenia were reported.

Thrombocytopenia of any degree should be monitored closely. If the platelet count falls below 100,000/mm³, ARIXTRA should be discontinued.

PRECAUTIONS

General

ARIXTRA Injection should be administered according to the recommended regimen, especially with respect to the timing of the first dose after surgery. In clinical studies, the administration of ARIXTRA before 6 hours after surgery has been associated with an increased risk of major bleeding (See ADVERSE REACTIONS: Hemorrhage and DOSAGE AND ADMINISTRATION).

ARIXTRA Injection should be used with care in patients with a bleeding diathesis, uncontrolled arterial hypertension or a history of recent gastrointestinal ulceration, diabetic retinopathy, and hemorrhage.

ARIXTRA (fondaparinux sodium) Injection should be used with caution in elderly patients (see **PRECAUTIONS: Geriatric Use**).

ARIXTRA should be used with caution in patients with a history of heparin-induced thrombocytopenia.

ARIXTRA Injection should not be mixed with other injections or infusions.

If thrombotic events occur despite ARIXTRA prophylaxis, appropriate therapy should be initiated.

Laboratory Tests

Periodic routine complete blood counts (including platelet count), serum creatinine level, and stool occult blood tests are recommended during the course of treatment with ARIXTRA Injection.

When administered at the recommended prophylaxis dose, routine coagulation tests such as Prothrombin Time (PT) and Activated Partial Thromboplastin Time (aPTT) are relatively insensitive measures of ARIXTRA activity, and are therefore, unsuitable for monitoring.

The anti-Factor Xa activity of fondaparinux sodium can be measured by anti-Xa assay using the appropriate calibrator (fondaparinux). Since the international standards of heparin or LMWH are not appropriate calibrators, the activity of fondaparinux sodium is expressed in milligrams (mg) of the fondaparinux and cannot be compared with activities of heparin or low molecular weight heparins (see **CLINICAL PHARMACOLOGY: Pharmacodynamics and Pharmacokinetics** and **WARNINGS: Laboratory Testing**).

Drug Interactions

In clinical studies performed with ARIXTRA, the concomitant use of oral anticoagulants (warfarin), platelet inhibitors (acetylsalicylic acid), NSAIDs (piroxicam) and digoxin did not significantly affect the pharmacokinetics/pharmacodynamics of fondaparinux sodium. In addition, ARIXTRA neither influenced the pharmacodynamics of warfarin, acetylsalicylic acid, piroxicam and digoxin, nor the pharmacokinetics of digoxin at steady state.

Agents that may enhance the risk of hemorrhage should be discontinued prior to initiation of ARIXTRA therapy. If co-administration is essential, close monitoring may be appropriate.

In an *in vitro* study in human liver microsomes, inhibition of CYP2A6 hydroxylation of coumarin by fondaparinux (200 μ M i.e., 350 mg/L) was 17–28%. Inhibition of the other isozymes evaluated (CYPs 2A1, 2C9, 2C19, 2D6, 3A4, and 3E1) was 0–16%. Since fondaparinux does not markedly inhibit CYP450s (CYP1A2, CYP2A6, CYP2C9, CYP2C19, CYP2D6, CYP2E1 or CYP3A4) *in vitro*, fondaparinux sodium is not expected to significantly interact with other drugs *in vivo* by inhibition of metabolism mediated by these isozymes.

Since fondaparinux sodium does not bind significantly to plasma proteins other than ATIII, no drug interactions by protein-binding displacement are expected.

Carcinogenesis, Mutagenesis, Impairment of Fertility

No long-term studies in animals have been performed to evaluate the carcinogenic potential of fondaparinux sodium.

Fondaparinux sodium was not genotoxic in the Ames test, the mouse lymphoma cell (L5178Y/TK^{+/−}) forward mutation test, the human lymphocyte chromosome aberration test, the rat hepatocyte unscheduled DNA synthesis (UDS) test, or the rat micronucleus test.

At subcutaneous doses up to 10 mg/kg/day (about 32 times the recommended human dose based on body surface area) fondaparinux sodium was found to have no effect on fertility and reproductive performance of male and female rats.

Pregnancy

Teratogenic Effects

Pregnancy Category B. Reproduction studies have been performed in pregnant rats at subcutaneous doses up to 10 mg/kg/day (about 32 times the recommended human dose based on body surface area)

and pregnant rabbits at subcutaneous doses up to 10 mg/kg/day (about 65 times the recommended human dose based on body surface area) and have revealed no evidence of impaired fertility or harm to the fetus due to fondaparinux sodium. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers

Fondaparinux sodium was found to be excreted in the milk of lactating rats. However, it is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when fondaparinux sodium is administered to a nursing mother.

Pediatric Use

Safety and effectiveness of ARIXTRA in pediatric patients have not been established.

Geriatric Use

ARIXTRA should be used with caution in elderly patients. Over 2300 patients, 65 years and older, have received fondaparinux sodium 2.5 mg in randomized clinical trials of peri-operative prophylaxis in orthopedic surgery. The efficacy of ARIXTRA in the elderly (equal to or older than 65 years) was similar to that seen in younger patients (younger than 65 years). The risk of ARIXTRA-associated major bleeding increased with age: 1.8% (23/1253) in patients < 65 years, 2.2% (24/1111) in those 65–74 years, and 2.7% (33/1227) in those ≥75 years. Serious adverse events increased with age for patients receiving ARIXTRA. In patients undergoing three weeks of extended prophylaxis following one week of peri-operative prophylaxis after hip fracture surgery, the incidence of major bleeding was: 1.9% (1/52) in patients <65 years, 1.4% (1/71) in those 65-74 years, and 2.9% (6/204) in those ≥75 years. Careful attention to dosing directions and concomitant medications (especially antiplatelet medication) is advised (see **CLINICAL PHARMACOLOGY** and **PRECAUTIONS: General**).

Fondaparinux sodium is substantially excreted by the kidney, and the risk of toxic reactions to ARIXTRA may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, it may be useful to monitor renal function (see **CONTRAINDICATIONS** and **WARNINGS: Renal Impairment**).

ADVERSE REACTIONS

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. The adverse reaction information from clinical trials does, however, provide a basis for identifying possible adverse events and for approximating rates.

The data described below reflect exposure in 5150 patients randomized to ARIXTRA (fondaparinux sodium) Injection in controlled trials of hip fracture, hip replacement, or major knee surgeries. Patients received ARIXTRA primarily in two large peri-operative dose-response trials (n=989), four active-controlled peri-operative trials with enoxaparin sodium (n=3616), and an extended prophylaxis trial (n=327) (see **CLINICAL STUDIES**).

Hemorrhage

During ARIXTRA administration, the most common adverse reactions were bleeding complications (see **WARNINGS**).

The rates of major bleeding events reported during clinical trials with ARIXTRA 2.5 mg Injection are provided in Tables 5 and 6 below.

Table 5: Major Bleeding Episodes¹ in Randomized, Controlled, Hip Fracture, Hip Replacement and Knee Replacement Surgery Studies

Indications	Peri-Operative Prophylaxis (Day 1 to Day 7±1 post-surgery)		Extended Prophylaxis (Day 8 to Day 28±2 post-surgery)	
	Fondaparinux Sodium 2.5 mg SC once daily	Enoxaparin Sodium ^{2, 3}	Fondaparinux Sodium 2.5 mg SC once daily	Placebo SC once daily
Hip Fracture	18/831 (2.2%)	19/842 (2.3%)	8/327 (2.4 %) ⁴	2/329 (0.6 %)
Hip Replacement	67/2268 (3.0%)	55/2597 (2.1%)		
Knee Replacement	11/517 (2.1%) ⁵	1/517 (0.2%)		

1. Major bleeding was defined as clinically overt bleeding that was (1) fatal, (2) bleeding at critical site (eg. intracranial, retroperitoneal, intra-ocular, pericardial, spinal or into adrenal gland), (3) associated with re-operation at operative site, or (4) with a bleeding index (BI) ≥ 2 calculated as [number of whole blood or packed red blood cell units transfused - [(pre-bleeding) – (post-bleeding)] hemoglobin (g/dL) values].

2. Enoxaparin sodium dosing regimen: 30 mg every 12 hours or 40 mg once daily.

3. Not approved for use in patients undergoing hip fracture surgery

4. During noncomparative, unblinded peri-operative prophylaxis, major bleeding was reported in 22/737 (3.0%) patients. Fifteen (15) of these 22-patients continued to receive Arixtra in extended prophylaxis. After randomization, 4/327 (1.2%) patients experienced major bleeding for the first time.

5. P value versus enoxaparin sodium: <0.01, 95% confidence interval: [1.1%, 3.3%] in ARIXTRA group versus [0.0%, 1.1%] in enoxaparin sodium group.

Table 6: Bleeding Across Randomized, Controlled Hip Fracture, Hip Replacement and Knee Replacement Surgery Studies

	Peri-Operative Prophylaxis (Day 1 to Day 7±1 post-surgery)		Extended Prophylaxis (Day 8 to Day 28±2 post-surgery)	
	Fondaparinux Sodium 2.5 mg SC once daily	Enoxaparin Sodium ^{1, 2}	Fondaparinux Sodium 2.5 mg SC once daily	Placebo SC once daily
	N = 3616	N = 3956	N = 327	N = 329
Major bleeding ³	96 (2.7%)	75 (1.9%)	8 (2.4%) ⁴	2 (0.6%)
Fatal bleeding	0 (0.0%)	1 (<0.1%)	0 (0.0%)	0 (0.0%)
Non-fatal bleeding at critical site	0 (0.0%)	1 (<0.1%)	0 (0.0%)	0 (0.0%)
Re-operation due to bleeding	12 (0.3%)	10 (0.3%)	2 (0.6%)	2 (0.6%)
BI ≥ 2 ⁵	84 (2.3%)	63 (1.6%)	6 (1.8%)	0 (0.0%)
Minor bleeding ⁶	109 (3.0%)	116 (2.9%)	5 (1.5%)	2 (0.6%)

1. Enoxaparin sodium dosing regimen: 30 mg every 12 hours or 40 mg once daily.

2. Not approved for use in patients undergoing hip fracture surgery

3. Major bleeding was defined as clinically overt bleeding that was (1) fatal, (2) bleeding at critical site (eg. intracranial, retroperitoneal, intra-ocular, pericardial, spinal or into adrenal gland), (3) associated with re-operation at operative site, or (4) with a bleeding index (BI) ≥ 2.

4. During non-comparative, unblinded, peri-operative prophylaxis, two fatal bleeds were reported (one in a 50 kg patient, one in a severe renal failure patient).

5. BI ≥ 2: overt bleeding associated only with a bleeding index (BI) ≥ 2 calculated as [number of whole blood or packed red blood cell units transfused - [(pre-bleeding) - (post-bleeding)] hemoglobin (g/dL) values].

6. Minor bleeding was defined as clinically overt bleeding that was not major.

A separate analysis of major bleeding across all randomized, controlled, peri-operative, prophylaxis, clinical studies according to the time of the first injection of ARIXTRA after surgical closure was performed in patients who received ARIXTRA only post-operatively. In this analysis the incidences of major bleeding were as follows: < 4 hours was 4.8% (5/104), 4-6 hours was 2.3% (28/1196), 6-8 hours was 1.9% (38/1965). In all studies, the majority (≥75%) of the major bleeding events occurred during the first four days after surgery.

Thrombocytopenia: See **WARNINGS: Thrombocytopenia.**

Local Reactions: Mild local irritation (injection site bleeding, rash and pruritus) may occur following subcutaneous injection of ARIXTRA.

Elevations of Serum Aminotransferases: In the peri-operative prophylaxis randomized clinical trials of 7 ± 2 days asymptomatic increases in aspartate (AST [SGOT]) and alanine (ALT [SGPT]) aminotransferase levels greater than three times the upper limit of normal of the laboratory reference range have been reported in 1.7% and 2.6% of patients, respectively, during treatment with ARIXTRA 2.5 mg Injection versus 3.2% and 3.9%, of patients, respectively, during treatment with enoxaparin sodium 30 mg every 12 hours or 40 mg once daily enoxaparin sodium. Such elevations are fully reversible and are rarely associated with increases in bilirubin. In the extended prophylaxis clinical trial no significant differences in aspartate (AST [SGOT]) and alanine (ALT [SGPT]) aminotransferase levels between ARIXTRA 2.5 mg Injection and placebo treated patients were observed.

Since aminotransferase determinations are important in the differential diagnosis of myocardial infarction, liver disease, and pulmonary emboli, elevations that might be caused by drugs like ARIXTRA should be interpreted with caution.

Other

Other adverse events that occurred during treatment with ARIXTRA or enoxaparin sodium in clinical trials with patients undergoing hip fracture surgery, hip replacement surgery, or knee replacement surgery and that occurred at a rate of at least 2% in either treatment group, are provided in Table 7 below.

Table 7: Adverse Events Occurring in $\geq 2\%$ of ARIXTRA, Enoxaparin Sodium or Placebo Treated Patients Regardless of Relationship to Study Drug Across Randomized, Controlled, Hip Fracture Surgery, Hip Replacement Surgery or Knee Replacement Surgery Studies

Adverse events	Peri-Operative Prophylaxis (Day 1 to Day 7 \pm 1 post-surgery)		Extended Prophylaxis (Day 8 to Day 28 \pm 2 post-surgery)	
	Fondaparinux Sodium 2.5 mg SC once daily	Enoxaparin Sodium ^{1, 2}	Fondaparinux Sodium 2.5 mg SC once daily	Placebo SC once daily
	N = 3616	N = 3956	N = 327	N = 329
Anemia	707 (19.6%)	670 (16.9%)	5 (1.5%)	4 (1.2%)
Fever	491 (13.6%)	610 (15.4%)	1 (0.3%)	4 (1.2%)
Nausea	409 (11.3%)	484 (12.2%)	1 (0.3%)	4 (1.2%)
Edema	313 (8.7%)	348 (8.8%)	3 (0.9%)	2 (0.6%)
Constipation	309 (8.5%)	416 (10.5%)	6 (1.8%)	7 (2.1%)
Rash	273 (7.5%)	329 (8.3%)	2 (0.6%)	4 (1.2%)
Vomiting	212 (5.9%)	236 (6.0%)	2 (0.6%)	4 (1.2%)
Insomnia	179 (5.0%)	214 (5.4%)	3 (0.9%)	1 (0.3%)
Wound drainage increased	161 (4.5%)	184 (4.7%)	2 (0.6%)	0 (0.0%)
Hypokalemia	152 (4.2%)	164 (4.1%)	0 (0.0%)	0 (0.0%)
Urinary tract infection	136 (3.8%)	135 (3.4%)	13 (4.0%)	13 (4.0%)
Dizziness	131 (3.6%)	165 (4.2%)	2 (0.6%)	0 (0.0%)
Purpura	128 (3.5%)	137 (3.5%)	0 (0.0%)	0 (0.0%)
Hypotension	126 (3.5%)	125 (3.2%)	1 (0.3%)	0 (0.0%)
Confusion	113 (3.1%)	132 (3.3%)	4 (1.2%)	1 (0.3%)
Bullous eruption ³	112 (3.1%)	102 (2.6%)	0 (0.0%)	1 (0.3%)
Urinary retention	106 (2.9%)	117 (3.0%)	0 (0.0%)	1 (0.3%)
Hematoma	103 (2.8%)	109 (2.8%)	7 (2.1%)	1 (0.3%)
Diarrhea	90 (2.5%)	102 (2.6%)	6 (1.8%)	8 (2.4%)
Dyspepsia	87 (2.4%)	102 (2.6%)	1 (0.3%)	2 (0.6%)
Post-operative hemorrhage	85 (2.4%)	69 (1.7%)	2 (0.6%)	2 (0.6%)
Headache	72 (2.0%)	97 (2.5%)	0 (0.0%)	2 (0.6%)
Pain	62 (1.7%)	101 (2.6%)	0 (0.0%)	0 (0.0%)
Surgical site reaction	29 (0.8%)	41 (1.0%)	5 (1.5%)	8 (2.4%)
1. Enoxaparin sodium dosing regimen: 30 mg every 12 hours or 40 mg once daily. 2. Not approved for use in patients undergoing hip fracture surgery 3. Localized blister coded as bullous eruption				

In ongoing studies for other indications, major bleeding events include intracranial hemorrhage, cerebral hemorrhage and retroperitoneal hemorrhage.

OVERDOSAGE

Symptoms/Treatment

There is no known antidote for ARIXTRA (fondaparinux sodium) Injection. Overdose of ARIXTRA may lead to hemorrhagic complications. Overdosage associated with bleeding complications should lead to treatment discontinuation and initiation of appropriate therapy.

Data obtained in patients undergoing chronic intermittent hemodialysis suggest that ARIXTRA clearance can increase by 20% during hemodialysis.

DOSAGE AND ADMINISTRATION

ARIXTRA (fondaparinux sodium) Injection is administered by subcutaneous injection.

In patients undergoing hip fracture, hip replacement, or knee replacement surgery, the recommended dose of ARIXTRA is 2.5 mg administered by subcutaneous injection once daily. After hemostasis has been established, the initial dose should be given 6 to 8 hours after surgery. Administration before 6 hours after surgery has been associated with an increased risk of major bleeding. The usual duration of administration is 5 to 9 days, and up to 11 days administration has been tolerated. In patients undergoing hip fracture surgery, an extended prophylaxis course of up to 24 additional days is recommended. In patients undergoing hip fracture surgery, a total of 32 days (peri-operative and extended prophylaxis) has been tolerated. (see **CLINICAL STUDIES**, **WARNINGS: Laboratory Testing** and **ADVERSE REACTIONS**).

INSTRUCTIONS FOR USE

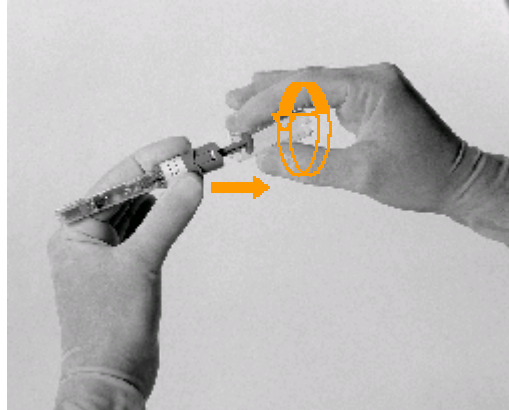
Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration.

ARIXTRA (fondaparinux sodium) Injection is provided in a single dose, prefilled syringe affixed with an automatic needle protection system. ARIXTRA is administered by subcutaneous injection. It must not be administered by intramuscular injections.

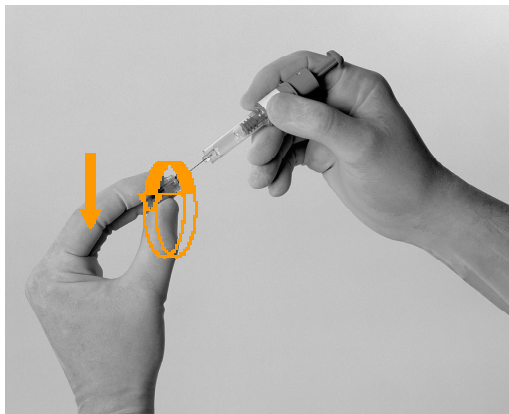
To avoid the loss of drug when using the pre-filled syringe, do not expel the air bubble from the syringe before the injection. Administration should be made in the fatty tissue, alternating injection sites (e.g., between the left and right anterolateral or the left and right posterolateral abdominal wall).

To administer ARIXTRA:

1. Wipe the surface of the injection site with an alcohol swab.
2. Twist the plunger cap and remove it.



3. Hold the syringe with either hand and use your other hand to twist the rigid needle guard (covers the needle) counter-clockwise. Pull the rigid needle guard straight off the needle.



4. Pinch a fold of skin at the injection site between your thumb and forefinger and hold it throughout the injection.

5. Hold the syringe with your thumb on the top pad of the plunger rod and your next two fingers on the finger grips on the syringe barrel. Pay attention to avoid sticking yourself with the exposed needle.



6. Insert the full length of the syringe needle perpendicularly into the skin fold held between the thumb and forefinger.



7. Push the plunger rod firmly with your thumb as far as it will go. This will ensure you have injected all the contents of the syringe.



8. When you have injected all the contents of the syringe, the plunger should be released. The plunger will then rise automatically while the needle withdraws from the skin and retracts into the security sleeve. Discard the syringe into the sharps container without replacing the rigid needle guard.
9. You will know that the syringe has worked when:
 - The needle is pulled back into the security sleeve and the white safety indicator appears above the blue upper body.
 - You may also hear or feel a soft click when the plunger rod is released fully.

HOW SUPPLIED

ARIXTRA (fondaparinux sodium) Injection is available in the following strength and package size:

Package of 10:

2.5 mg ARIXTRA in 0.5 mL single dose prefilled syringe, affixed with a 27-gauge x 1/2-inch needle with a blue automatic needle protection system

NDC 66203-2300-1

ARIXTRA™

Store at 25°C (77°F); excursions permitted to 15–30°C (59–86°F) [See USP Controlled Room Temperature].

Keep out of the reach of children.



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